

Cancer of the nasopharynx in Aotearoa New Zealand from 1994 to 2018: Incidence and survival in a population-based, national registry cohort study



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Summary

Background Cancer of the nasopharynx has remarkable geographic and ethnic variation in incidence and outcomes globally. Recent advances in diagnostic and therapeutic technologies provide new opportunities for early detection and improved outcomes. This study aimed to determine the incidence, demographics, outcomes and time trends of cancer of the nasopharynx in Aotearoa New Zealand over the last 25 years.

Methods In a population-based, national registry cohort study of notifications of malignant neoplasms of the nasopharynx made to the New Zealand Cancer Registry between 1994 and 2018, age-specific and age-standardised incidence rates and survival outcomes were evaluated.

Findings 577 registrations of nasopharyngeal cancer from between 1994 and 2018 were analysed; median age at diagnosis 54 years; 72.4% male; 37.4% Asian, 24.3% New Zealand European, 25.3% Pacific peoples, 13.0% Māori. Age-standardised annual incidence remained low (<1/100,000 person-years) and stable from 1994 to 2018. Age-standardised incidence rates in Pacific peoples, Asian and Māori were 21 (95% CI 12.07-35.21), 17 (10.95-25.33) and 4 (2.79-7.07)-fold higher, respectively, than New Zealand Europeans. Epstein-Barr virus-related morphologies predominated keratinising squamous cell carcinoma and not-otherwise-specified morphological subtypes. Ten-year overall survival rate for the cohort was 49.2% (95% CI 44.7-53.5). Older age at diagnosis (65–94 years), Māori or Pacific ethnicity, keratinising squamous cell carcinoma and distant disease were associated with shorter overall survival, whereas younger age at diagnosis (10-29 years), and Asian ethnicity were associated with longer survival.

Interpretation Aotearoa New Zealand has a distinct profile of nasopharyngeal cancer, with age, ethnicity and morphology among the main determinants of incidence and survival.

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Introduction

Nasopharyngeal cancer is known for remarkable geographic and ethnic variation in incidence and outcomes resulting from a complex interplay of viral, host genetic and environment causative factors.^{1,2} International data compiled from national cancer registry reports show that in Aotearoa New Zealand, like in the rest of the Western world, nasopharyngeal cancer is a relatively

uncommon malignancy.^{3–5} In contrast, nasopharyngeal cancer incidence is greatest in east and southeast Asia and elsewhere, particularly among Cantonese people of southern China and indigenous populations in South East Asia, Arctic, North Africa and the Middle East.^{2,4,6} Aotearoa New Zealand is a multi-ethnic society with 70.2% identifying as European, 16.5% indigenous Māori, 15.1% Asian and 8.1% with Pacific Island backgrounds. Many identify with more than one ethnic group and 27.4% were not born in Aotearoa New Zealand.⁷ Not only does nasopharyngeal cancer incidence have stark geographic variability, but there are differences in distribution by pathological subtype. Non-keratinising (NK)

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Research in context

Evidence before this study

International evidence describes a distinct geographic and ethnic variation in nasopharyngeal cancer epidemiology. There are few published studies on the epidemiology of nasopharyngeal cancer in Aotearoa New Zealand. We searched PubMed and Scopus from inception to 2021 with terms defined as “New Zealand” AND “nasopharyngeal” AND (“epidemiology” OR “incidence” OR “survival”). Three relevant articles were identified. One study reported nasopharyngeal cancer incidence over the period 1954–1991 but did not describe the cohort’s demographic or clinical characteristics. The two other studies were limited to the Auckland region. One of these reported that from 1976–1985 nasopharyngeal cancers disproportionately affected Māori, Pacific and Asian populations. The other reported differences in extent of disease at diagnosis by ethnicity.

Added value of this study

This is the first national-level whole of population evaluation of the burden of nasopharyngeal cancer in Aotearoa New Zealand describing incidence and survival outcomes. It finds that Aotearoa New Zealand has a distinct profile of nasopharyngeal cancer, with age, ethnicity and morphology among the main determinants of incidence and survival and highlights inequities, especially for Pacific peoples.

Implications of all the available evidence

Identification of the population groups most at risk of diagnosis with, and poor outcomes from, nasopharyngeal cancer provides direction for clinical practice changes to target those who could benefit most from early disease detection.

nasopharyngeal carcinoma, divided into differentiated and undifferentiated tumours, accounts for most cases in endemic parts of Asia, and is strongly associated with Epstein-Barr virus (EBV) infection. In contrast, keratinising squamous cell carcinoma of the nasopharynx accounts for less than 20% of cases worldwide and is relatively infrequent in endemic countries but often predominates in non-endemic regions and is associated with smoking.^{1,2}

Recent advances in the understanding of nasopharyngeal cancer risk factors and pathogenesis, and in the development of diagnostic and therapeutic technologies, have provided new opportunities for early detection and improved outcomes. The association of EBV viral and HLA host genotypes with increased susceptibility provide a basis for identifying individuals at high risk.³ Plasma EBV DNA detection has shown promise for screening at risk populations for early detection of asymptomatic disease.⁸ In established cases, plasma EBV DNA detection can aid risk stratification and

monitoring of treatment response.¹ Optimisation of radiotherapy and chemotherapy protocols, such as with intensity modulated radiation therapy (IMRT)⁹ and induction cisplatin-gemcitabine chemotherapy,¹⁰ have improved locoregional control and overall survival and reduced toxicity.^{9,11} In that context, there are currently few published data on demographic and clinical characteristics or the incidence of nasopharyngeal cancer at a national-level in Aotearoa New Zealand.¹² Previous research, limited to the Auckland region, reported that nasopharyngeal cancer disproportionately affects Māori, Pacific peoples and Asian populations^{13,14} and reported on differences in extent of disease at diagnosis.¹⁵ Ethnic diversification of Aotearoa New Zealand in recent decades coupled with advances in molecular detection, imaging techniques and optimised chemoradiation strategies underscores the importance of an updated review. Little is also known about survival outcomes for patients with nasopharyngeal cancer in Aotearoa New Zealand, and prognostic factors relevant to our population have not been defined.

As new diagnostic and therapeutic technologies have become available with the potential for earlier detection, more precise risk stratification and improved outcomes, it is important to acquire information about the current demographic profile, incidence and outcomes of nasopharyngeal cancer in the local population. Therefore, in the current study, we performed a review of 25 years of nasopharyngeal cancer registrations to describe its demographic profile, clinicopathological characteristics, incidence, time trends and survival outcomes in Aotearoa New Zealand between 1994 to 2018.

Methods

Study design and data source

We undertook a retrospective review of registrations of malignant neoplasms of the nasopharynx over a 25-year period from 1994 to 2018 in the New Zealand Cancer Registry (NZCR). The NZCR is the central repository for all new cancer diagnoses (excluding non-melanoma skin cancers) in Aotearoa New Zealand, as mandated by the Cancer Registry Act 1993.¹⁶ We included all registrations of malignant neoplasms of the nasopharynx (ICD-7 code 146; ICD-8 code 147; ICD-9-CM code 147, ICD-10 code C11) between 1 January 1994 and 31 December 2018. Exclusion criteria included: date of diagnosis outside 1994–2018, no histological diagnosis, or recurrent disease including recurrent tumour at the site of previous nasopharyngeal cancer or new metastatic disease on the background of a previous nasopharyngeal cancer. Malignant neoplasms of soft tissue or minor salivary glands, melanoma and neuroendocrine tumours were excluded. Registrations with unknown ethnicity or domicile code were excluded. For survival analyses, cases diagnosed at death or post-mortem were excluded.

Registrations and variable selection

Individual level data for the following variables were extracted: diagnosis date (defined as the date of the first pathological report confirming nasopharyngeal cancer), cancer event ID (a unique registry entry code), age at diagnosis, sex, prioritised ethnicity, domicile code, morphological code, disease extent (NZCR extent of disease or The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) staging) and date of death. NZCR data were not independently verified (as this study was of de-identified data and did not include clinical notes review).

Demographic characteristics

Age at diagnosis was grouped into 10-29 years, 30-64 years and 54-94 years to form groups representing young, middle and older ages with sufficient numbers for analysis and aid comparison to previously published international data.¹⁷⁻²⁰ Ethnicity was classified into Māori, Pacific, Asian or New Zealand European, and prioritized ethnicity was used if a registration listed multiple ethnicities (patients with more than one recorded ethnicity were allocated to a single ethnic group in order of priority: Māori, Pacific, Asian and New Zealand European).²¹

Domicile codes were linked to District Health Boards (DHBs), and DHBs were grouped into one of four regions that corresponded to regional cancer networks, i.e. the Northern, Midland, Central and Southern regions. The Northern region covers the Northland, Auckland, Counties Manukau and Waitemata DHBs. The Midland region covers Waikato, Lakes, Bay of Plenty and Tairāwhiti DHBs. The Central region covers Taranaki, Whanganui, MidCentral, Hawke's Bay, Wairarapa, Hutt Valley and Capital and Coast DHBs. The Southern region encompasses the whole of the South Island.

Domicile code was also used to assign deprivation level (a geographic area-based measure of deprivation coded 1-10 from areas of least to highest deprivation²²) using the NZDep index (NZDep91, NZDep96, NZDep2001, NZDep2006 and NZDep2013) from the same year that the NZCR would have been used for the domicile code.^{22,23} Deprivation level was grouped into NZDep 1-4, 5-7 and 8-10.

Registrations were grouped into three diagnostic time periods comprising approximately equal numbers of registrations. The earliest diagnostic period included registrations made between 28 January 1994 to 14 May 2003, the middle diagnostic period between 22 May 2003 to 8 March 2011 and the latest diagnostic period between 24 March 2011 to 19 December 2018.

Tumour characteristics

Morphology codes were classified into keratinising squamous cell carcinoma (KSCC) (ICD-O codes 8070 and 8071), differentiated non-keratinising carcinoma

(DNKC) (ICD-O codes 8072 and 8073), undifferentiated non-keratinising carcinoma (UNKC) (ICD-O codes 8020, 8021, 8082, and 8083) and not otherwise specified (NOS) (ICD-O codes 8000 (neoplasm, malignant), as well as 8010 (carcinoma not otherwise specified)). Registrations without histological diagnosis may have been included in the NOS group.

Registrations up to 1997 were coded by NZCR extent of disease staging. These are 0 (in situ), 1 (localised), 2 (regional or node involvement), 3 (remote or diffuse metastases), or 5 (not stated). Registrations from 1998 onwards were coded with The National Cancer Institute's SEER staging definitions.²⁴ SEER codes are B (limited to organ of origin), C (extension to adjacent organs), D (extension to regional lymph nodes), E (distant metastases) and F (unknown). For analysis, NZCR and SEER coding were merged into three categories: NZCR 0, 1 and 2 with SEER B, C and D ('local/regional'), NZCR 3 with SEER E ('distant disease/metastatic') and NZCR 5 with SEER F ('unknown').

Statistical analysis

Four patients, whose ethnicity was other than Asian, Pacific, Māori or New Zealand European, were removed from the final analysis. For the remaining registrations (n=577), the number and proportion of registrations were summarized by demographic (age, sex, ethnicity, deprivation, cancer region and diagnostic period) and pathological (morphological subtype and extent of disease) characteristics. Differences between groups were examined with Chi-squared tests with *P* values <0.05 being statistically significant.

Nasopharyngeal cancer incidence rates were calculated as the annual number of cases per 100,000 person-years, and presented for early, middle and late diagnostic periods, using the New Zealand resident population from the 1996, 2006 and 2013 censuses, respectively.²⁵ Using the whole cohort, incidence rates were calculated for each age group (age-specific incidence rates). Age-standardised incidence rates were estimated by subgroups (morphology, sex and ethnicity), referencing the WHO world standard population.²⁶ 95% confidence intervals were calculated.²⁷ Differences in incidence rates between groups were regarded as being statistically significant when their 95% confidence intervals did not overlap.

For survival analyses, follow up time was calculated as the time from the diagnosis date to end of the study date (23 October 2019). Median follow up time was 12.5 years (range 0.84 – 25.7 years). Overall survival was calculated from the diagnosis date. Two patients with dates of death the same as their diagnosis date were excluded from the survival analysis. Patients with no known date of death were censored on the end of study date (23 October 2019). The Kaplan-Meier method was used to estimate the overall survival by age, sex,

ethnicity, morphology, disease extent and diagnostic period, and comparisons between survival curves were made with log rank tests. Five-year relative survivals were calculated as the ratio of the 5-year observed Kaplan-Meier survival to mean 5-year expected survival for the whole cohort and for each subgroup (age, sex, ethnicity, morphology, diagnosis period and disease extent). The expected survival was estimated by matching the individual patients to general population by age at diagnosis, birth year and sex using New Zealand population life tables.²⁸ 95% confidence intervals of relative survival ratios were calculated.²⁹

Associations of survival outcomes with demographic and tumour characteristics were evaluated using univariable and multivariable Cox regression models to compute hazard ratios and 95% confidence intervals. Estimates were considered statistically significant for the values of $P < 0.05$. All data analyses were performed in Stata v16.1 and Microsoft Excel.

Ethics: This observational study of existing de-identified registry data was deemed not to require formal National Health and Disability Ethics Committee approval (out of scope for formal review). Local research institutional approval was granted by the Auckland DHB Research Review Committee (A+8707).

Results

Demographic and clinicopathological characteristics

A total of 635 registrations of malignant neoplasms of nasopharynx were made to the NZCR between 1st January 1994 and 31st December 2018 (Figure 1). After exclusion of 36 registrations of malignant neoplasms of soft tissue or minor salivary glands, melanoma or neuroendocrine tumours, 18 registrations with missing values, and 4 patients of ethnicity other than Asian, Pacific, Māori or New Zealand European, a cohort of 577 eligible patients remained with a median of 24 registrations per year (range 15–33) over the 25-year study period.

The demographic and clinicopathological characteristics of the retrospective cohort of 577 eligible patients are depicted in Table 1. The majority of cases (399/577, 69.2%) were diagnosed in the 30–64 year age group, with a median age at diagnosis of 54 years. 72.4% (418/577) were male. The cohort comprised 37.4% (216/577) Asian, 24.3% (140/577) New Zealand European, 25.3% (146/577) Pacific peoples and 13.0% (75/577) Māori. The majority of cases were the non-keratinising morphological subtypes (221/577 [38.3%] undifferentiated non-keratinising carcinoma or 87/577 [15.1%] differentiated non-keratinising carcinoma), while fewer were keratinising squamous cell carcinoma (133/577 [23.1%]) or the not-otherwise-specified morphological subtypes (136/577 [23.6%]). It was unknown how many of the NOS group had no histological diagnosis. Staging information was unknown for 48.2% (278/577) of cases.

Demographic factors varied between different nasopharyngeal cancer morphology subtypes (Table 1). Keratinising squamous cell carcinoma presented more frequently in the older (65–94 years) age group, in New Zealand European and Māori, outside of the Northern region, and in the earliest (1994–2003) diagnostic period. Differentiated non-keratinising and undifferentiated non-keratinising carcinomas presented more frequently in the middle (30–64 years) age group, in Pacific peoples and Asian, in the Northern region, and in the later (2011–2018) diagnostic period. See supplementary table 1 for a breakdown of characteristics by ethnicity.

Incidence

Overall, there was a crude incidence rate per 100,000 person-years of 0.58 (95% CI 0.57–0.58) compared to a WHO age-standardised incidence rate per 100,000 person-years of 0.49 (95% CI 0.45–0.53). For the cohort as a whole, there were no significant changes in crude (range 0.57 [95% CI 0.54–0.60] - 0.61 [95% CI 0.58–0.64]) or age-standardised (range 0.48 [95% CI 0.41–0.55] - 0.52 [95% CI 0.45–0.60]) incidence rates with time between the three diagnostic periods. Poisson regression resulted in a coefficient for diagnosis year of 0.01 (95% CI 0 - 0.02) supporting that the trend was stable. However, incidence rates varied markedly between different subgroups. By age (Figure 2 A), age-specific incidence rates were lowest in the younger (10–29 years) age group (0.1 [95% CI 0.09–0.1]), highest in the older (65–90 years) age-group (1.12 [95% CI 1.08–1.16]) and intermediate in the middle (30–64 years) age group (0.87 [95% CI 0.85–0.88]). With time, age-specific incidence rates increased in the younger (10–29 years) age group and decreased in the older (65–90) age group (Figure 2A). Males had higher age-standardised incidence (0.72 [95% CI 0.65–0.79]) than females (0.27 [95% CI 0.23–0.32]) (Figure 2C). By ethnicity (Figure 2D), Pacific peoples had the highest age-standardised incidence (3.43 [95% CI 2.85–4.01]), followed by Asian (2.77 [95% CI 2.38–3.16]) then Māori (0.74 [95% CI 0.56–0.92]), with the lowest rate in New Zealand European (0.17 [95% CI 0.14–0.20]). The incidence of nasopharyngeal cancer in different sex and ethnicity subgroups was largely unchanged with time except for a recent decrease in Asian patients. Among morphological subtypes, there were variable trends over time, with an increasing incidence of differentiated non-keratinising carcinoma, stable incidences of keratinising squamous cell carcinoma and undifferentiated non-keratinising carcinoma, and a decreasing incidence of nasopharyngeal cancer not-otherwise-specified.

Survival outcomes

Median follow up time was 12.5 years (range 0.84–25.7 years). For the cohort as a whole, median overall



Figure 1. Flow diagram of the identification of eligible registrations.

* 36 excluded registrations included adenoid cystic carcinoma¹⁰, adenocarcinoma, not otherwise specified⁵, malignant melanoma⁴, embryonal rhabdomyosarcoma, not otherwise specified³, neuroendocrine carcinoma, not otherwise specified³, papillary adenocarcinoma, not otherwise specified², clear chordoma, not otherwise specified², small cell carcinoma, not otherwise specified¹, cell adenocarcinoma, not otherwise specified¹, rhabdomyosarcoma, not otherwise specified¹, alveolar rhabdomyosarcoma¹, cellular leiomyoma¹, synovial sarcoma, biphasic¹, oligodendroglioma, not otherwise specified¹, ^ 18 excluded registrations included registrations of unknown ethnicity¹⁰, unknown domicile code⁸, # 4 excluded registrations with ethnicity other than Asian, Pacific, Māori or New Zealand European included Middle Eastern², African¹, Latin American/Hispanic¹.

survival was 9.3 years (95% CI 6.4–12.5 years) (Figure 3A). Kaplan–Meier and log-rank tests showed significant differences in overall survival by age (Figure 3B), ethnicity (Figure 3C), morphology (Figure 3D), and disease extent (Figure 3E). Overall survival was significantly longer in subgroups with younger age at diagnosis, Asian ethnicity, nasopharyngeal cancer morphologies other than keratinising squamous cell carcinoma, and locoregional or unknown disease extent. Conversely, overall survival was significantly shorter in

subgroups with older age at diagnosis, non-Asian ethnicity, keratinising squamous cell carcinoma, and distant disease.

Five-year overall survival rate (Table 2), for the cohort as a whole, was 57.7% (95% CI 53.4–61.8) and the 10-year overall survival rate was 49.2% (95% CI 44.7–53.5). Five-year overall survival rates were higher for the younger (10–29 years) age group (86.6% [95% CI 70.8–94.2]) and lower for the older (65–94 years) age group (30.0% [95% CI 22.4–37.9]) compared to the middle

		Total		Keratinising Squamous Cell Carcinoma		Differentiated Non-Keratinising Carcinoma		Undifferentiated Non-Keratinising Carcinoma		Not Otherwise Specified*		P**
		N	%	n	%	n	%	n	%	n	%	
	Total	577	100.0	133	100.0	87	100.0	221	100.0	136	100.0	
Age	10-29 y	40	6.9	5	3.8	4	4.6	22	10.0	9	6.6	<0.001
	30-64 y	399	69.2	83	62.4	69	79.3	166	75.1	81	59.6	
	65-94 y	138	23.9	45	33.8	14	16.1	33	14.9	46	33.8	
Sex	Male	418	72.4	94	70.7	67	77.0	164	74.2	93	68.4	0.460
	Female	159	27.6	39	29.3	20	23.0	57	25.8	43	31.6	
Ethnicity	NZ European	140	24.3	54	40.6	15	17.2	34	15.4	37	27.2	<0.001
	Māori	75	13.0	28	21.1	16	18.4	23	10.4	8	5.9	
	Pacific	146	25.3	27	20.3	23	26.4	62	28.1	34	25.0	
	Asian	216	37.4	24	18.1	33	37.9	102	46.2	57	41.9	
Deprivation	NZDep 1-4	164	28.4	37	27.8	23	26.4	62	28.1	42	30.9	0.298
	NZDep 5-7	162	28.1	32	24.1	28	32.2	56	25.3	46	33.8	
	NZDep 8-10	251	43.5	64	48.1	36	41.4	103	46.6	48	35.3	
Region	Northern	326	56.5	44	33.1	55	63.2	141	63.8	86	63.2	<0.001
	Midland	85	14.7	37	27.8	8	9.2	27	12.2	13	9.6	
	Central	105	18.2	30	22.6	13	14.9	41	18.6	21	15.4	
	Southern	61	10.6	22	16.5	11	12.6	12	5.4	16	11.8	
Diagnosis period	1994-2003	192	33.3	54	40.6	8	9.2	53	24.0	77	56.6	<0.001
	2003-2011	192	33.3	41	30.8	21	24.1	91	41.2	39	28.7	
	2011-2018	193	33.5	38	28.6	58	66.7	77	34.8	20	14.7	
Disease extent	Local/regional	212	36.7	49	36.8	40	46.0	85	38.5	38	27.9	0.060
	Distant/metastatic	87	15.1	22	16.5	10	11.5	26	11.8	29	21.3	
	Unknown	278	48.2	62	46.6	37	42.5	110	49.8	69	50.7	

Table 1: Demographic and clinicopathological characteristics of the Aotearoa New Zealand nasopharyngeal cancer cohort by morphological subtype.

* including 74 registrations of "neoplasm, malignant" and 67 registrations of "carcinoma, not otherwise specified".

** P values are from Chi squared tests.

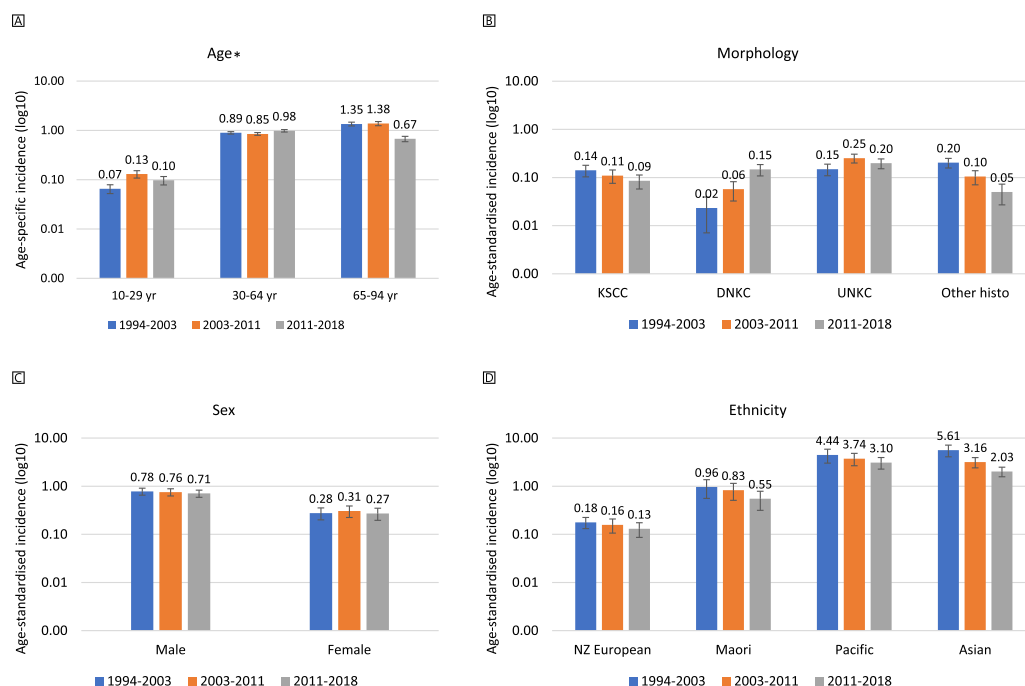


Figure 2. Population-based incidence rates (in log₁₀ scale) of nasopharyngeal cancer in Aotearoa New Zealand by age at diagnosis (A), morphology (B), sex (C), morphology (D) and diagnostic period. Bars represent means and error bars for the 95% confidence intervals for age-specific (A) or age-standardised incidence rates (B, C, D) (annual cases per 100,000). KSCC, keratinising squamous cell carcinoma; DNKC, differentiated non-keratinising carcinoma; UNKC, undifferentiated non-keratinising carcinoma; NOS, non-otherwise specified. Age, ethnicity and sex were among the main determinants of variation in nasopharyngeal cancer incidence.

(30–64 years) age group (64.3% [95% CI 59.2–69.0]). Five-year overall survival rates were higher for Asian (74.5% [95% CI 67.8–80.0]) than other ethnicities. Five-year overall survival rates were lower for keratinising squamous cell carcinoma (38.2% [95% CI 29.7–46.5]) than other nasopharyngeal cancer morphological subtypes. Five-year overall survival rates were lower for those with distant disease at diagnosis (36.2% [95% CI 26.0–46.4]) than for those with locoregional or unknown disease extent. These differences remained significant after calculation of relative 5-year survival rates (Table 2) that adjusted for expected background mortality by age and sex.

Factors associated with overall survival

Variables significantly associated with overall survival on univariable analysis (Table 3) were age, sex, ethnicity, deprivation, region, diagnostic period, morphology and disease extent. On multivariable analysis (Table 3), age, ethnicity, morphology, disease extent and diagnostic period remained independent and significant factors impacting on overall survival. Older age at diagnosis (HR=2.75 [95% CI 2.15–3.52]), Māori ethnicity (HR 2.21 [95% CI 1.46–3.36]), Pacific ethnicity (HR 2.10 [95% CI 1.50–2.92]), New Zealand European (HR 1.84 [95% CI 1.31–2.61]), keratinising squamous cell carcinoma

(HR=1.72 [95% CI 1.27–2.33]) and distant disease (HR=1.74 [95% CI 1.25–2.40]) were associated with increased risk of death, whereas younger age at diagnosis (HR=0.30 [95% CI 0.14–0.63]), and earlier diagnostic period (1994–2003) (HR=0.74 [95% CI 0.56–0.97]) were associated with reduced risk of death. A global test for proportional hazards assumptions yielded $p=0.0001$. We ran the Cox models separated by three defined periods (not reported), and the HRs in all three models remained similar to those in the main model. Therefore, we report the main model only.

Discussion

Our study provides the first national-level whole of population evaluation of the burden of nasopharyngeal cancer in Aotearoa New Zealand. Our results can be viewed in the context of current understanding of the distinct ethnic and geographic distribution of nasopharyngeal cancer globally as has been described by international data and previous studies from elsewhere.^{1,2,4,5} In Aotearoa New Zealand, it was known from annual reports from the NZCR³ that the incidence of nasopharyngeal cancer was low compared to other cancers, but the characteristics and outcomes of the patient population affected by nasopharyngeal cancer had not been described.

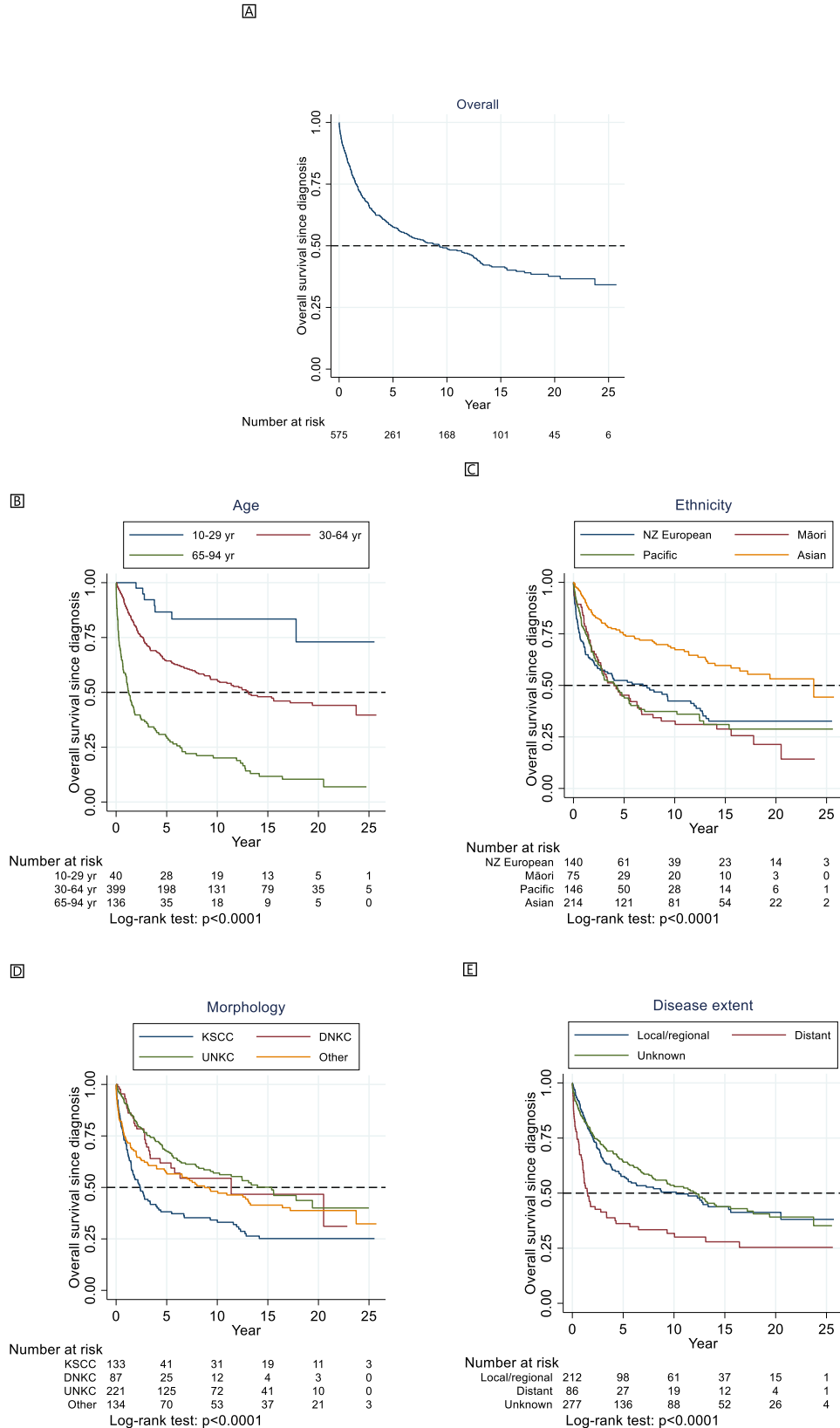


Figure 3. Overall survival from nasopharyngeal cancer in Aotearoa New Zealand. Survival curves are shown for the cohort as a whole (A), and by age at diagnosis (B), ethnicity (C), morphology (D) and disease extent (E) as the main determinants of overall survival.

	N	Absolute 5-year Overall Survival		Relative 5-year Overall Survival*		
		%	(95% CI)	%	(95% CI)	
Total	577	57.7	(53.4-61.8)	61.4	(57.1-65.7)	
Age	10-29 years	40	86.6	(70.8-94.2)	86.9	(76.3-97.5)
	30-64 years	399	64.3	(59.2-69.0)	65.8	(61.0-70.6)
	65-94 years	138	30.0	(22.4-37.9)	37.0	(27.6-46.4)
Sex	Male	418	54.7	(49.6-59.6)	58.8	(53.7-64.0)
	Female	159	65.4	(57.3-72.4)	68.0	(60.3-75.7)
Ethnicity	NZ European	140	52.4	(43.6-60.4)	59.1	(49.8-68.4)
	Māori	75	45.3	(33.5-56.3)	47.8	(35.9-59.7)
	Pacific	146	44.8	(36.2-53.0)	47.1	(38.6-55.6)
	Asian	216	74.5	(67.8-80.0)	77.5	(71.4-83.5)
Deprivation	NZDep 1-4	164	68.3	(60.2-75.1)	72.9	(65.3-80.6)
	NZDep 5-7	162	59.9	(51.7-67.2)	64.4	(56.3-72.5)
	NZDep 8-10	251	49.7	(43.1-55.9)	52.4	(45.9-59.0)
Region	Northern	326	59.1	(53.3-64.4)	62.8	(57.1-68.5)
	Midland	85	48.6	(37.5-58.9)	52.1	(40.7-63.5)
	Central	105	65.0	(54.4-73.7)	67.6	(58.1-77.1)
	Southern	61	50.9	(37.5-62.8)	56.5	(42.6-70.4)
Diagnosis Period	1994-2003	192	58.6	(51.3-65.2)	63.6	(56.0-71.1)
	2003-2011	192	52.1	(44.8-58.9)	55.3	(47.8-62.8)
	2011-2018	193	63.4	(55.2-70.6)	66.5	(59.4-73.6)
Morphology	KSCC	133	38.2	(29.7-46.5)	41.2	(32.3-50.1)
	DNKC	87	61.9	(48.8-72.5)	64.6	(54.0-75.3)
	UNKC	221	67.6	(60.8-73.5)	70.4	(64.0-76.8)
	NOS	136	57.4	(48.4-65.3)	63.3	(54.1-72.5)
Disease extent	Local/regional	212	57.6	(50.4-64.2)	60.8	(53.8-67.9)
	Distant	87	36.2	(26.0-46.4)	39.1	(28.2-50.0)
	Unknown	278	64.5	(58.4-70.1)	68.8	(62.8-74.8)

Table 2: Five-year absolute and relative survival rates for the Aotearoa New Zealand nasopharyngeal cancer cohort as a whole, and for subgroups defined by age at diagnosis, ethnicity, morphology, disease extent and diagnosis period.

N, sample size; HR, CI, confidence intervals; KSCC, keratinising squamous cell carcinoma; DNKC, differentiated non-keratinising carcinoma; UNKC, Undifferentiated non-keratinising carcinoma; NOS, not otherwise specified.

* relative survival rates were adjusted for expected background mortality by age and gender.

Our study showed a distinct pattern of nasopharyngeal cancer in Aotearoa New Zealand compared to elsewhere. The overall incidence of nasopharyngeal cancer in Aotearoa New Zealand was low, with a median of 24 registrations per year, and age-standardised incidence rates per 100,000 person-years for men (0.72) and women (0.27) were consistent with international data from other non-endemic countries.^{1,2,4,5} However, unlike other countries, where the incidence of nasopharyngeal cancer is decreasing by approximately 1% per year,^{5,17,30,31} the age-standardised incidence rate of nasopharyngeal cancer in Aotearoa New Zealand remained unchanged over a 25-year period. In addition, we found significant ethnic disparities, with nasopharyngeal cancer age-standardised incidence rates that were 21-fold higher for those of Pacific ethnicity, 17-fold-higher for Asian and 4-fold higher for Māori, compared to New Zealand European. This differs from previous data limited to the Auckland region that reported a higher

nasopharyngeal cancer incidence in patients of Chinese rather than Pacific ethnicity.¹³ Importantly, this shows that in Aotearoa New Zealand, the greatest burden of nasopharyngeal cancer falls on patients of Pacific ethnicity. Other reports from elsewhere linked Asian and Pacific ethnicities together,³⁰ which risked missing ethnic-specific differences when studying heterogeneous groups in aggregate. To our knowledge, this is one of the first studies from a non-endemic region to have shown the incidence of nasopharyngeal cancer to be highest in a non-Asian ethnic group. Despite nasopharyngeal cancer being considered non-endemic in Aotearoa New Zealand, the majority of cases in our study were non-keratinising morphologies, which are the dominant subtypes in endemic areas and those associated with EBV infection.^{1,2} Unlike other non-endemic settings, such as the United States where keratinising squamous cell carcinoma often predominates,^{18,30,31} we found keratinising squamous cell carcinoma in only

		N	Univariable			Multivariable		
			HR	95% CI	P	HR	95% CI	P
Age	10-29 y	40	0.31	(0.14-0.65)	0.002	0.30	(0.14-0.63)	0.002
	30-64 y	399	1.00		Ref	1.00		Ref
	65-94 y	138	3.21	(2.53-4.07)	<0.001	2.75	(2.15-3.52)	<0.001
Sex	Male	418	1.00		Ref	1.00		Ref
	Female	159	0.72	(0.55-0.94)	0.017	0.83	(0.63-1.10)	0.201
Ethnicity	NZ European	140	2.23	(1.63-3.05)	<0.001	1.84	(1.31-2.61)	0.001
	Māori	75	2.55	(1.79-3.63)	<0.001	2.21	(1.46-3.36)	<0.001
	Pacific	146	2.41	(1.77-3.28)	<0.001	2.10	(1.50-2.92)	<0.001
	Asian	216	1.00		Ref	1.00		Ref
Deprivation	NZDep 1-4	164	0.68	(0.51-0.90)	0.008	0.93	(0.68-1.27)	0.630
	NZDep 5-7	162	0.89	(0.68-1.16)	0.390	1.02	(0.77-1.35)	0.908
	NZDep 8-10	251	1.00		Ref	1.00		Ref
Region	Northern	326	1.00		Ref	1.00		Ref
	Midland	85	1.48	(1.09-2.03)	0.013	0.87	(0.60-1.26)	0.449
	Central	105	0.97	(0.71-1.33)	0.856	0.89	(0.64-1.25)	0.509
	Southern	61	1.47	(1.04-2.10)	0.031	1.12	(0.77-1.63)	0.557
Diagnosis Period	1994-2003	192	0.88	(0.67-1.14)	0.317	0.74	(0.56-0.97)	0.031
	2003-2011	192	1.00		Ref	1.00		Ref
	2011-2018	193	0.71	(0.52-0.97)	0.030	0.75	(0.55-1.04)	0.082
Morphology	KSCC	133	2.13	(1.60-2.83)	<0.001	1.72	(1.27-2.33)	<0.001
	DNKC	87	1.07	(0.71-1.59)	0.757	0.96	(0.63-1.45)	0.830
	UNKC	221	1.00		Ref	1.00		Ref
	Other	136	1.39	(1.03-1.88)	0.031	1.26	(0.92-1.73)	0.157
Disease extent	Local/regional	212	1.00		Ref	1.00		Ref
	Distant	87	1.92	(1.39-2.63)	<0.001	1.74	(1.25-2.40)	0.001
	Unknown	278	0.93	(0.72-1.20)	0.592	0.92	(0.71-1.20)	0.543

Table 3: Univariable and multivariable analysis of factors associated with overall survival (measured as mortality HR, hazard ratios) of the Aotearoa New Zealand nasopharyngeal cancer cohort.

N, sample size; HR, CI, confidence intervals; KSCC, keratinising squamous cell carcinoma; DNKC, differentiated non-keratinising carcinoma; UNKS, Undifferentiated non-keratinising carcinoma; NOS, not otherwise specified.

23.1% of cases. Furthermore, the age-standardised incidence rates of keratinising squamous cell carcinoma and undifferentiated non-keratinising carcinoma in our study remained unchanged with time, unlike elsewhere, where significant time-dependent changes in rates of these morphology subtypes have been reported.^{30,31} Although this study demonstrated stable time trends and striking variation by ethnicity, it did not address factors underlying these distinct patterns of nasopharyngeal cancer incidence in Aotearoa New Zealand. In our study, the apparent increase over time in incidence of differentiated non-keratinising carcinoma and decrease in incidence of nasopharyngeal carcinoma not otherwise specified may reflect changes in pathological practices for classifying nasopharyngeal cancer rather than real changes in disease incidence. As reported elsewhere,^{5,31,32} age and sex were also determinants of the nasopharyngeal cancer incidence in the Aotearoa New Zealand population. The higher registration count seen in the Northern region is likely due to the higher

proportion of Asian and Pacific peoples domiciled in this part of Aotearoa New Zealand.

Age, ethnicity and morphology were among the major determinants of overall survival in the Aotearoa New Zealand nasopharyngeal cancer cohort. The median overall survival of about 10 years and 5-year survival rate of about 60% was comparable to outcomes from other national population-based registry datasets.^{18,30,31,33} For example, the US National Cancer Institute reports a 5 year relative survival rate for all nasopharyngeal cancer stages combined of 61%(19) compared to 61.4% in our study. The finding on multivariable analysis that age, ethnicity, morphology and disease extent all significantly impacted survival was also broadly consistent with international data.^{18,30,33} For example, the survival advantage of morphologies other than keratinising squamous cell carcinoma and for patients of Asian ethnicity compared to other ethnicities has also been reported elsewhere.^{18,30} Not only did Pacific peoples have the highest incidence of

nasopharyngeal cancer, but their survival outcomes were numerically the poorest out of any ethnic group in our study. The lack of detailed information about clinical stage at presentation or subsequent access to treatment, hindered further investigation into reasons behind those poor outcomes for Pacific patients. Age at diagnosis has consistently been found to be associated with survival outcomes in population-based studies of nasopharyngeal cancer.^{20,33,34} In our study, age was the strongest prognostic factor with approximately 3-fold increases or decreases in risk of death in the youngest and oldest age groups, respectively, compared to the middle-age group. Survival outcomes were not significantly improved in the most recent diagnostic period, despite introduction of newer radiation therapy techniques, combined modality treatment protocols and other improvements in clinical practice. As expected survival outcomes were poorer in patients presenting with distant disease. In support of targeted screening for at risk Pacific peoples, the age-standardised incidence rate per 100,000 person-years of 3.43 for Pacific peoples in Aotearoa New Zealand was similar to that reported from high-risk geographical regions elsewhere, such as Thailand (2.1) and Philippines, Manila (3.5), but lower than in Singapore (7.1) and Hong Kong (9.5).⁵

The findings of the current study have implications for the development of healthcare policy and clinical practice changes to address the poor outcomes and inequities caused by nasopharyngeal cancer in Aotearoa New Zealand. The finding that advanced disease at diagnosis is a strong adverse prognostic factor highlights the potential importance of earlier detection. Currently, there is no targeted screening program for nasopharyngeal cancer in Aotearoa New Zealand. However, plasma EBV DNA analysis was shown to be a potentially useful screening test for detecting early stage asymptomatic nasopharyngeal cancer in an at risk population in Hong Kong with 97.1% sensitivity and 98.6% specificity.⁸ Clinical practice guidelines now recommend screening of high risk populations.³⁵ Plasma EBV testing is not yet widespread or common practice for early detection of nasopharyngeal cancer. Its adoption will need to consider the costs and organisation required, as well as defining the target group for screening. There is now a particular need to consider the feasibility of targeted screening in the Aotearoa New Zealand context. Based on the findings of this study, targeted screening could perhaps be best considered for Pacific patients who have the highest incidence and poorest outcomes from nasopharyngeal cancer in Aotearoa New Zealand.

This study had a number of strengths and limitations, inherent in the data used. As the data is based on a legally-mandated national cancer registry, with international standards of completeness and quality control, the study population was fully representative as it comprised all nasopharyngeal cancer registrations made in Aotearoa New Zealand over 25 years. The dataset had nearly

complete demographic and mortality data. However, the variables available for analysis were limited to those collected routinely during the process of cancer registration. Therefore, clinical staging information was unavailable and registry-based stage categorization based on pathology reports were available for only about half of the registrations. Moreover, the national registry does not include detailed treatment or clinical management information, or outcomes other than mortality. EBV tumour status was not available in the registry dataset. These limitations meant that we could not evaluate cancer-specific survival, distant metastasis-free survival or relapse-free survival, relapse patterns, or short-term and long-term treatment related complications, such as stroke, radiation-associated second malignancies and aspiration pneumonia. We could not assess treatment, such as types of radiation used. The addition of EBV status in the NZCR would be optimal given the modern understanding of its role as an aetiological factor and prognostic and predictive biomarker.¹

In conclusion, our study has shown a distinct profile of nasopharyngeal cancer in Aotearoa New Zealand. Age, ethnicity and morphology were among the main determinants of variations in nasopharyngeal cancer incidence and survival outcomes in Aotearoa New Zealand. In the future, collection of prospective data, including EBV tumour status, clinical stage, treatment information and nasopharyngeal cancer specific outcomes could aid further understanding of the epidemiology of nasopharyngeal cancer in Aotearoa New Zealand. Identification of population groups most at risk of nasopharyngeal cancer and locally-relevant prognostic factors could guide new healthcare policy development and clinical practice changes to improve disease prevention and care for those most in need.

Contributors

Alice Minhinnick: conceptualisation, data curation, investigation, methodology, project administration, writing (original draft), writing (review & editing). Phyu Aye: formal analysis, methodology, visualisation, writing (original draft, review & editing). Mark Elwood: supervision, writing (review & editing). Mark McKeage: conceptualisation, formal analysis, methodology, supervision, visualisation, writing (original draft), writing (review & editing).

Data sharing statement

The data for this study were provided by the New Zealand Ministry of Health, and may be available to other researchers who meet data access requirements. Please contact data_enquiries@moh.govt.nz for further details on eligibility and data provision.

Declaration of interests

The authors have no conflicts to disclose.

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Supplementary materials

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